Remarks

Entry of the following response, as well as reconsideration and withdrawal of the rejections of record, is respectfully requested.

Summary of Status of Amendment and Office Action

In the present amendment, no claim is cancelled, amended, or added. Therefore, claims 8-26 remain pending in the application.

In the Office Action dated March 18, 2008, claims 13-15 and 18-26 are deemed allowable, but are objected to as depending from rejected base claims. Claims 8-12, 16 and 17 are rejected under 35 U.S.C. § 103 (a) as obvious in view of Fahrig et al. (WO 96/23506, English translation). The March 18 Office Action does not maintain the July 2, 2007, indefiniteness rejection of the claims under 35 U.S.C. § 112.

Response to Objections to Claims 13-15 and 18-26

Applicants thank the Examiner for indicating that claims 13-15 and 18-26 recite patentable subject matter. These claims are not amended herein to eliminate dependency on rejected base claims because, for the reasons explained below, it is respectfully submitted that all pending claims are patentable.

Response to Rejection of Claims 8-12, 16 and 17 as Obvious

As an initial matter, the arguments concerning non-obviousness submitted in the Amendment dated November 26, 2007, are incorporated herein in their entirety, and are supplemented for emphasis below.

The Office Action maintains the rejection of claims 8-12, 16 and 17 under 35 U.S.C. § 103 (a) as obvious in view of Fahrig et al. (WO 96/23506, English translation) (hereinafter, "the Fahrig PCT"). In reply to the Amendment filed November 26, 2007, the Office Action

acknowledges that the Fahrig PCT does not disclose administering a 5' substituted nucleoside (e.g., BVDU) during a recovery phase after a cytostatic chemotherapy cycle. The Office Action asserts that administering a 5' substituted nucleoside during such a recovery phase would be obvious in view of the Fahrig PCT because the document teaches that concurrent administration of BVDU and a cytostatic agent reduces the build-up of resistance to cytostatic treatment. It is the position in the rejection that since the Fahrig PCT discloses that BVDU and/or its metabolites can reduce build-up of resistance in cytostatic treatment, it would have been obvious to administer BVDU after administration of cytostatics during a recovery phase.

Moreover, in response to Applicants' arguments submitted on November 26, 2007, the Office Action states that administration of a 5' substituted nucleoside during a recovery phase would be obvious in view of the Fahrig PCT because the document indicates that BVDU alone appears to slightly lessen the degree of spontaneous gene amplification in clinically relevant doses.

In response, it is respectfully submitted that the Examiner is under a mistaken impression regarding the significance of gene amplification discussed in the Fahrig PCT, and that a proper understanding of this principle actually emphasizes the unobvious and unexpected nature of the presently-claimed invention.

Specifically, reduction in gene amplification is not an indication for spontaneous apoptosis, but is just an explanation for an enhanced take-up of cytostatics. That is, a reduction in gene amplification indicates that cytostatic agents will not be shuttled out of the cells as efficiently, thereby making the cytostatic agent more effective ***when the cytostatic agent is present in the cell.*** As can be seen from this, the portion of the Fahrig PCT cited in the Office Action (page 10, line 24 to page 11, line 3) only serves as an explanation of the efficacy of a 5'

substituted nucleoside in the presence of a cytostatic agent — ***it does not explain, or even suggest, the increased apoptosis observed when a 5' substituted nucleoside is administered during a recovery phase <u>after</u> a cytostatic chemotherapy cycle.***

Therefore, based on the teachings in the Fahrig PCT, one of ordinary skill in the art would only have expected a 5' substituted nucleoside such as BVDU to be effective when administered during a cytostatic chemotherapy cycle. More to the point, because of the inhibitory effect that 5' substituted nucleosides have on gene amplification (i.e., on shuttling cytotoxic agents out of cancer cells), ***one of ordinary skill in the art would have expected such compounds not to have any significant effect if administered during a recovery phase after a cytostatic chemotherapy cycle.***

For these reasons, the Fahrig PCT, if anything, suggests to those of skill in the art that administration of a 5' substituted nucleoside during a recovery phase would be ineffective. Therefore, as seen from the English translation, the Fahrig PCT teaches away from administering a 5' substituted nucleoside during a recovery phase. By teaching away from the present invention, the present invention is unobvious over the Fahrig PCT.

Even if the Office Action had established a *prima facie* case of obviousness (which Applicants maintain is not the case), the present application contains sufficient unexpected results to overcome the rejection. The Federal Circuit has stated that "unexpected results may be sufficient to rebut a *prima facie* case of obviousness." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed.Cir.2006); see also *In re De Blauwe*, 736 F.2d 699, 706 n. 8 (Fed.Cir.1984) ("A proper showing of unexpected results will rebut a prima facie case of obviousness."). "The basic principle behind this [rule] is straightforward — that which would have been surprising to a

person of ordinary skill in a particular art would not have been obvious." *In re Mayne*, 104 F.3d 1339, 1343 (Fed.Cir.1997).

The present application presents the surprising discovery that administration of a 5' substituted nucleoside during a recovery phase unexpectedly provides better chemotherapeutic results than where there is no such administration during the recovery phase. See Paragraph **[0014]** and **[0016]** - **[0019]** of the published application.

Moreover, Applicant has additional unexpected results that are included as an attachment to this Amendment. The unexpected results include results presented in co-pending U.S. Patent Application Ser. No. 11/853,540 (made of record in the Supplemental Information Disclosure Statement filed concurrently with this Amendment). The Examiner is invited to review Application Ser. No. 11/853,540 and/or to review the Attachment. If the Examiner so requires, then the Attachment can be put into the form of a Declaration under 37 C.F.R. 1. 132.

As seen in the Attachment (which in places employs the term RP101 for BVDU) tumors in rats actually grew faster when the rats were treated with BVDU in the absence of chemotherapy (Attachment, page 1, lines 6-10). Moreover, BVDU exhibited a small benefit in rats when administered only on the same day as the cytostatic agent (Attachment, page 2, lines 20-22). However, when included in a regimen including BVDU administration during the recovery phase, there was a strong anti-tumor effect (Attachment, page 3, lines 5-21).

More importantly, the unexpected beneficial effect of BVDU administered during the recovery phase is also seen in clinical (human) studies (Attachment, page 5, line 28 to page 8, line 10). In fact, in patients stricken with pancreatic cancer (one of the most lethal cancers known), administration of BVDU during the recovery phase in clinical studies approximately doubled the patients' survival times (Attachment, page 8, lines 12-13).

These results are especially surprising in view of the theory presented in the Fahrig PCT, which would not lead one of ordinary skill in the art to administer a 5' nucleoside during a recovery phase.

Accordingly, the present application provides sufficient unexpected results to overcome a *prima facie* case of obviousness, had the Office Action established such a rejection (which Applicants maintain is not the case).

For at least the above reasons, the Fahrig PCT does not teach or suggest administering a 5' nucleoside (e.g., BVDU) during a recovery phase after a cytostatic chemotherapy cycle. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the obviousness rejection of claims 8-12, 16 and 17.

Conclusion

For the reasons advanced above, Applicants respectfully submit that all pending claims patentably define Applicants' invention. Allowance of the application with an early mailing date of the Notices of Allowance and Allowability is therefore respectfully requested.

Should there be any questions, the Examiner is invited to contact the undersigned at the below listed telephone number.

Respectfully submitted,

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